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METHYLPHENIDATE AND PEMOLINE: EFFECTS ON SLEEPINESS AND MOOD DURING SLEEP DEPRIVATION

L.T. MATTESON
T.L. KELLY
H. BABKOFF
S. HAUSER
P. NAITOH

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NAVAL HEALTH RESEARCH CENTER
P.O. BOX 85122
SAN DIEGO, CALIFORNIA 92186-5122

NAVAL MEDICAL RESEARCH AND DEVELOPMENT COMMAND
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EFFECTS ON SLEEPINESS AND MOOD DURING SLEEP DEPRIVATION

Larry T. Matteson

Tamsin L. Kelly

Harvey Babkoff

Sheri Hauser

Paul Naitoh

Naval Health Research Center

P.O. Box 85122

San Diego, California 92138-9174

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Summary

The purpose of the present study was to examine the effect of non-amphetamine stimulants on subjective and objective measures of sleepiness and mood during a 64-hour sleep loss period. Subjects were thirty-six male adult non-smokers (mean age = 20.94) from the Basic Underwater Demolition (BUDS) and SEAL training program. The subjects received methylphenidate (10 mg every 6 hours; 8 doses), pemoline (37.5 mg every 12 hours; 4 doses), or placebo beginning at 2200 hours on the first night of sleep deprivation. Subjective sleepiness was measured by the "alertness" subscale of the Visual Analog Scale, and was administered every 3 hours during the sleep loss period. The objective measure was the frequency of lapses (inter-tap interval > 3 seconds), during a 10 minute tapping task, and was administered every 6 hours. Mood was measured by the Profile of Mood States (POMS), and was administered every 3 hours. Analysis indicated that 37.5 mg pemoline administered every 12 hours significantly reduces both subjective and objective sleepiness in our subjects, primarily during the circadian trough periods which occur during the early morning and early afternoon hours, but has little effect on self ratings of mood. Conversely, 10 mg methylphenidate demonstrated negligible effects on these measures. The non-addictive nature of pemoline may explain it's lack of effect on mood.

INTRODUCTION

The reduction of sleep loss effects in military personnel can be essential to the success of military missions. The data from a variety of laboratories indicate that long term sleep deprivation results in changes in perceptual, cognitive, and psychomotor performance, as well as subjective psychological ratings. Stimulants have been used in an number of studies to try to maintain or revive performance and to prevent dangerous lapses in wakefulness during prolonged sleep loss. Recently military pilots have been prescribed amphetamines when required to fly long missions with no rest (Howard, 1966). Amphetamines have demonstrated improvements in human performance in fatigued subjects (e.g., Holliday and Devery, 1968; Newhouse et al, 1989). However, the abuse potential and adverse physiological effects resulting from the extended use of amphetamines limit their applicability.

The stimulants methylphenidate and pemoline were chosen as possible alternatives to the amphetamines for use during extended periods of wakefulness. These drugs have been used primarily in the treatment of attention deficit disorder and narcolepsy (Conners and Taylor, 1980; Mitler et al., 1986). Both drugs have been shown to be effective in reversing the effects of fatigue on performance (Gelfand et al., 1968, Orzack et al., 1968).

Methylphenidate is a piperidine derivative which facilitates the release of catecholamines, and blocks their re-uptake and degradation. It is thought to activate in the brain stem arousal system of the cortex. It has a relatively short half-life of one to two hours, and the duration of action is approximately four to six hours. Testing in normal adults has shown that methylphenidate can significantly improve alertness, reaction times, and vigilance.

Pemoline is an oxizolidine compound. It acts primarily through catecholamine uptake inhibition in the central nervous system (Molina and Orsingher, 1981). Pemoline has less sympathomimetic cardiovascular effects than methylphenidate, and requires less frequent dosing due to its longer half life of approximately 12 hours (Barnhart, 1988). Significant amelioration of performance degradation has been reported after a single dose of pemoline in normal adults (Orzack, 1968; Haward, 1970). In contrast to the amphetamines, pemoline has little or no abuse potential (Langer et al., 1986).

Some studies involving stimulants have administered drugs after extended periods of wakefulness in an attempt to ameliorate the negative effect of sleep loss. In the present study, stimulants were administered in a "preventative" approach, and the effects of methylphenidate and pemoline in the maintenance of behavior during sleep loss were analyzed. Results on the effects of stimulants and sleep loss on performance variables are presented in a separate report. This paper focuses on the effects of methylphenidate and pemoline on subjective and objective measures of sleepiness and mood.

METHODS

Subjects:

Subjects were 36 healthy young adult male volunteers, mean age 20.94 $\pm$ 2.74 (range 18-28), from the Basic Underwater Demolition (BUDS) and SEAL training program. Subjects were non-smokers and consumed no more than three cups of caffeinated beverage per day (approx 150 mg). Subjects completed a health and sleep questionnaire, and gave informed consent after receiving a detailed explanation of the protocol.

Treatments:

The 36 subjects were randomly assigned in equal numbers to 1 of 3 groups in a parallel-group, double-blind design (see Table 1). The control group received placebo capsules every 6 hours for a total of 8 capsules. The methylphenidate group received 10 mg methylphenidate every 6 hours for a total of 8 doses. The pemoline group received 37.5 mg pemoline every 12 hours for 4 doses, with placebo capsules given at alternate 6 hour intervals. Drug or placebo administration in all groups commenced at 2200 hours on the first night of sleep deprivation.

TABLE 1.

Treatment Groups

Group	Dosage
Placebo	Placebo every 6 hours X 8
Methylphenidate	10 mg every 6 hours X 8
Pemoline	37.5 mg every 12 hours X 4

Sleepiness and Mood Measures:

Both subjective and objective sleepiness were measured. The subjective measure of sleepiness was a computerized version of the Sleepiness/Alertness subscale of the Visual Analog Scale; the objective measure was the frequency of lapses during a 10 minute tapping task. Mood was measured by the Profile

of Mood States (POMS). The VAS and POMS were administered every 3 hours during the 64-hour sleep loss period. The tapping task was administered every other session (every six hours) during the sleep loss period.

VAS:

The Visual Analog Scale was used to establish a subjective rating of sleepiness. The task consisted of a linear scale ranging from "Very Sleepy" to "Very Alert". The subject moved a pointer to a position along the thirty point continuum which represented his current level of Sleepiness/Alertness.

LAPSES:

A 10-minute tapping task was used to objectively measure sleepiness. This was an adoption of a similar tapping task which was shown to correlate significantly with sleep latency as measured by the Multiple Sleep Latency Test (Johnson, et al., 1990). The subject was seated in a comfortable chair with his eyes open, his arm supported and his index finger resting on the key. He was instructed to relax but stay awake and to tap a key at the rate of about once per second. A lapse was scored when the time between taps was longer than 3 seconds. If there was an interval greater than 10 seconds, the computer beeped to remind the subject to continue tapping, or to wake him if he had fallen asleep. The task is a measure of ability to remain awake and, in that respect, is similar to the Maintenance of Wakefulness Test (MWT) (Mitler et al., 1982).

Profile of Mood States (POMS):

The POMS is a computerized version of the Educational and Industrial Testing Service POMS (McNair, Lorr, and Droppleman, 1971). It consists of a series of words describing mood. The subject responds with a number from 0 to 4 depending on how closely each word describes his current mood: 0 = "not at all", 1 = "a little", 2 = "moderately", 3 = "quite a bit", 4 = "extremely".

The subscales of the POMS measure degree of Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, Confusion-Bewilderment, Positive, and Total Mood Disturbance.

Procedures:

The size of the groups varied due to subject availability, ranging from 2 to 4 subjects per experimental run. ANOVA for repeated measures indicated that group size had no significant effects on sleepiness or mood. Subjects remained in the laboratory for 4 days while participating in the study. Caffeinated foods and beverages were excluded from the diet during the experimental period. The first morning consisted of training, the following afternoon baseline measurements were recorded. Follow-up training occurred during that evening for subjects who had not achieved an acceptable level of accuracy. Subjects slept in the laboratory Monday night and the 64-hour sleep deprivation period commenced at 0620 hours Tuesday morning. Subjects were constantly monitored by technicians who wakened them if they fell asleep. Blood pressure, pulse, and temperature were also monitored every 2 hours during the sleep loss period.

Statistical Analysis:

Data was initially analyzed via 3-way ANOVA for repeated measures (Group X Time X Day) covering the 48 hour period of drug administration. Significant main effects and/or interactions were further defined with appropriate post-hoc analysis. Due to exceptionally poor performance, one subject in the methylphenidate group was excluded from all analysis. It was felt that this individual did not adhere to the requirements of the study (e.g., he completed only 2 addition problems in a 20 minute session with 50% accuracy).

RESULTS

VAS:

The ANOVA for repeated measures indicated a significant Time X Group interaction for VAS ($F(14, 224) = 1.83$, $p < .04$). Post-hoc analysis demonstrated that only pemoline reduced subjective sleepiness, and it did so predominately during the circadian troughs (0200-0600 hours). Subjects receiving pemoline were significantly less sleepy than placebo subjects on both night 1 ($t(21.4) = -2.35$, $p < .03$), and night 2 ($t(22) = -2.05$, $p < .05$). Subjects receiving pemoline were significantly less sleepy than subjects receiving methylphenidate during night 2 ($t(19.5) = -2.32$, $p < .05$), and during the afternoon dip (1300-1400 hours) on both day 2 ($t(19.9) = -2.37$, $p < .03$) and day 3 ($t(18.6) = -2.27$, $p < .04$) (see Figures 1 & 2).

Lapses:

The large number of 0's (sessions with no lapses) in the lapse data produced a distribution significantly different from the Guassian. Therefore, the non-parametric Kruskal-Wallis analysis was used. Results from this analysis indicated that there were significant group differences overall ($H(34) = 6.55$, $p < .04$). Paired group comparisons showed that subjects receiving pemoline ranked significantly lower in number of lapses than subjects who received methylphenidate overall ($H(23) = 5.88$, $p < .02$). The most pronounced drug effect occurred at the circadian trough of the first night where subjects who received pemoline had significantly fewer lapses than subjects who received methylphenidate ($H(22) = 9.38$, $p < .002$). A similar trend was found with pemoline vs placebo ($H(23) = 3.24$, $p < .07$). Subjects receiving pemoline also ranked lower in number of lapses than subjects who received placebo during the following afternoon ($H(23) = 3.89$, $p < .05$) (see Figure 3).

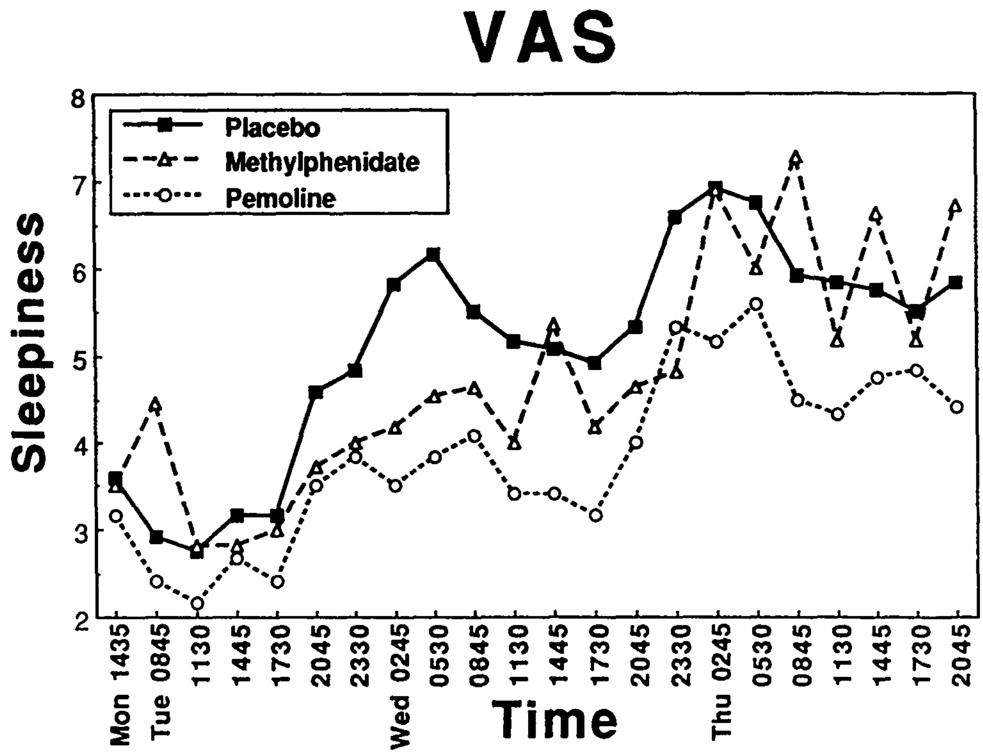

Figure 1. Mean subjective sleepiness rating.

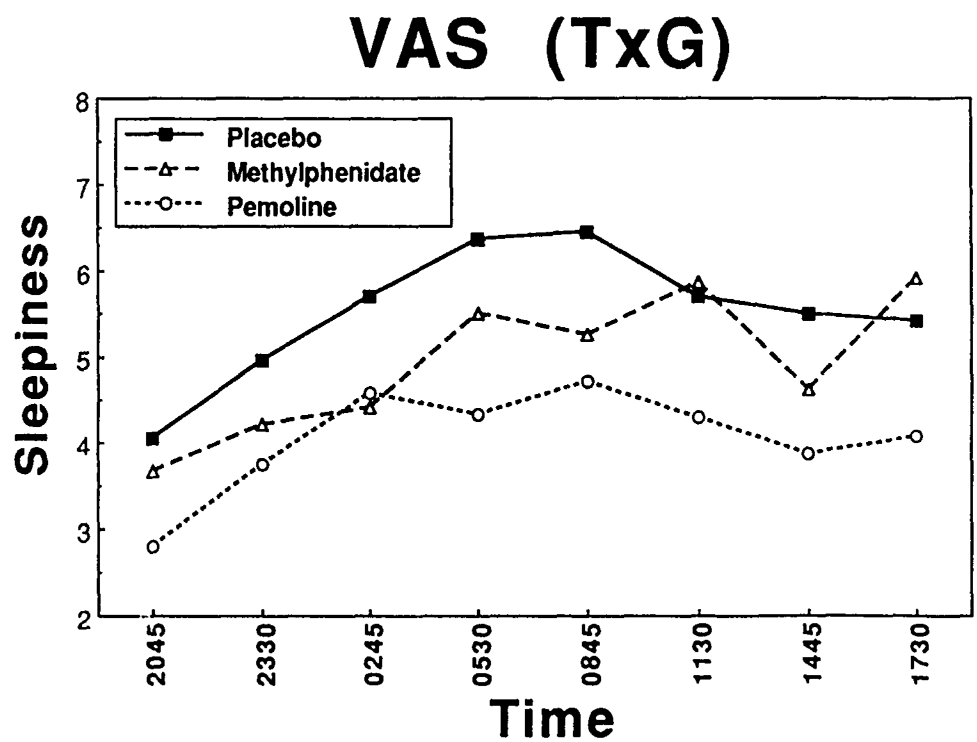

Figure 2. Mean subjective sleepiness rating (Collapsed by day).

To determine any relationship between drug effects and duration of task, the data from the first five minutes was compared to the second five minutes and the difference score was analyzed by ANOVA for repeated measures. Results from this analysis failed to show significant main effects or group interactions on this difference score. Pearson analysis showed a highly significant correlation between the first and second five minute intervals overall ($r = .91$, $p < .0001$). Trial by trial analysis demonstrated that this relationship was maintained throughout the sleep loss period.

<u>Mood</u>:

Repeated measures ANOVA for POMS failed to discover any main effects or 2-way interactions with drug for any of the subscales. A significant 3-way interaction (Group X Time X Day) was found with the "vigor" subscale ($F(14, 224) = 2.38$, $p < .004$). However, subsequent post-hoc analysis failed to show significant group differences for any time on either day, or with both days combined.

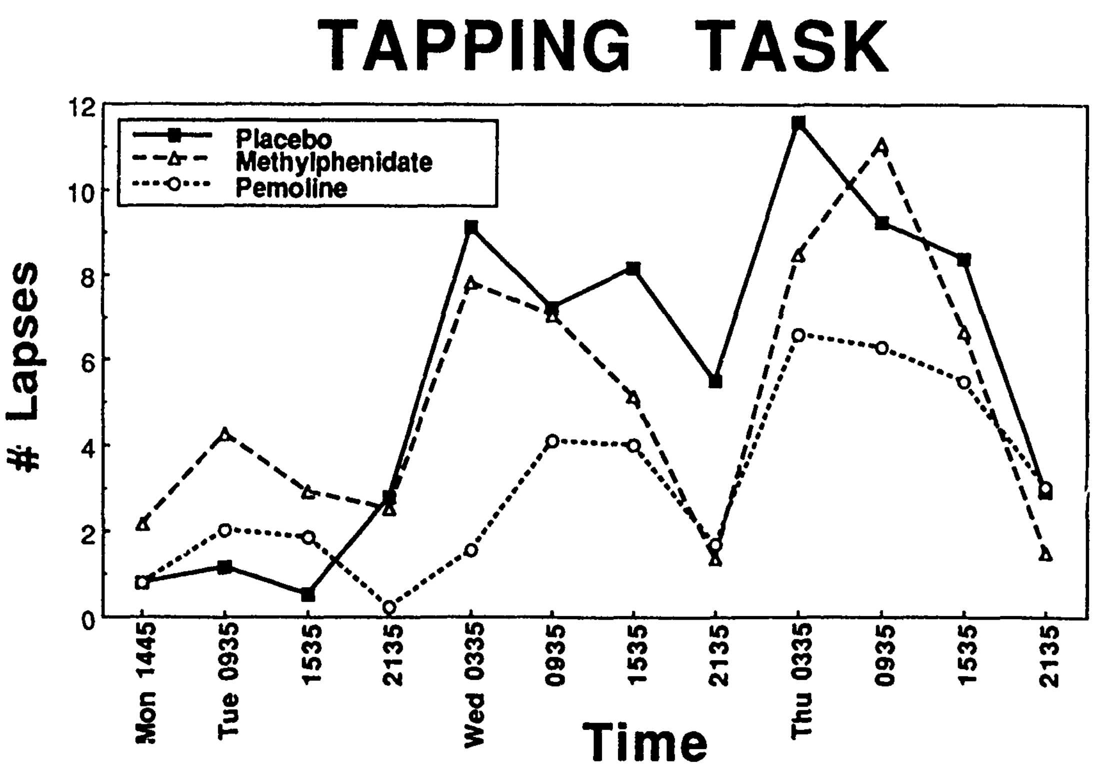

Figure 3 . Mean number of lapses >3 sec. during a 10 min. tapping task.

DISCUSSION

Moderate doses of pemoline significantly reduced the levels of objective and subjective sleepiness in our population. These effects occurred primarily through the reduction of the increased sleepiness caused by the circadian troughs. These effects continued throughout the entire 64-hour period for subjective sleepiness ratings, but only during the first 32 hours for the objective measure. This pattern of timing of effects was similar to that seen in pemoline's effects on speed of performance (data presented elsewhere). In contrast, the methylphenidate and placebo groups did not differ significantly from one and other for either sleepiness measure. Thus, the effectiveness of methylphenidate for countering sleepiness at this dose level is limited. Similarly, methylphenidate failed to maintain performance speed or accuracy on a number of tasks.

Given pemoline's marked effect on sleepiness and performance measures, it's lack of effect on mood,is of interest. Other studies involving stimulant drugs and sleep loss have found significant correlations between performance and mood. When performance is enhanced by stimulants, mood, in general, is similarly effected. Newhouse et al. (1989), found that 20-mg as well as 10-mg amphetamine produced significant (although short lived) group differences from placebo on the "vigor" and "fatigue" subscales of the POMS after 48 hours of sleep loss. These changes in mood corresponded to the changes observed on a number of performance measures.

There are various possible explanations for this lack of effect on mood. It is possible that the lack of group differences may be due to our unique subject population. Our subjects were participants in the Naval Special

Warfare (BUDS) training program. These men had undergone training that conditioned their bodies and minds to handle extensive physical and psychological stress. A consequence of this training may be a degree of insensitivity to, or suppression of, feelings, emotions and, therefore, mood. Such lack of sensitivity could make it quite difficult to detect group differences on the POMS, or any mood measure, regardless of experimental intervention.

An alternative explanation could relate to the moderate dose of pemoline that was administered in this study. As mentioned earlier, Newhouse et al. (1989) found that 10 and 20-mg amphetamine significantly altered mood. In contrast, there were negligible effects with a 5-mg dose. Perhaps a higher dose of pemoline will produce significant mood effects even in this population. A future study employing different doses of pemoline will determine the dose response characteristics of these effects. However, pemoline differs from both the amphetamines and methylphenidate in that it is not addictive, not a drug of abuse. As a non-addictive drug, it is probably less likely to show mood effects at any dose.

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Thirty-six male subjects (mean age = 20.94) participated in a study of the effects of methylphenidate (10 mg every 6 hours; 8 doses) or pemoline (37.5 mg every 12 hours; 4 doses) in maintaining alertness during 64 hours of sleep deprivation. Subjective sleepiness was measured by a Visual Analog Scale (VAS), objective sleepiness by the number of lapses (intertap inverval 3 seconds) on a 10 minute tapping task, and mood by the Profile of Mood States (POMs). Results indicate that 37.5 mg pemoline administered every 12 hours significantly reduced both subjective and objective sleepiness in sleep deprived subjects. Primarily during the circadian throughs but has little effect on self ratings of mood; while 10 mg of methylphenidate administered every 6 hours has no significant effect on these measures.

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